Effect of Intra-articular Ketorolac Versus Corticosteroid Injection for Knee Osteoarthritis

A Retrospective Comparative Study

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Background: Intra-articular corticosteroid injections have been widely used and are considered a mainstay in the nonoperative treatment of symptomatic knee osteoarthritis (OA). However, their increased use can have negative implications, including chondral toxicity and a high risk of infections. As a result, nonsteroidal anti-inflammatory drugs have been considered as an alternative.

Purpose: To determine the pain relief and safety of ketorolac versus a corticosteroid to supplement an intra-articular sodium hyaluronate injection for the treatment of symptomatic knee OA.

Study Design: Cohort study; Level of evidence, 3.

Methods: A total of 84 patients with unilateral symptomatic knee OA receiving 5 weekly injections were enrolled in this retrospective study. Group A (n = 42) received 3 weekly intra-articular corticosteroid injections (0.5% lidocaine, 25 mg of triamcinolone acetonide, and 25 mg of sodium hyaluronate, followed by 2 weekly injections of 0.5% lidocaine and 25 mg of sodium hyaluronate), while group B (n = 42) received 5 weekly ketorolac injections (0.5% lidocaine, 10 mg of ketorolac, and 25 mg of sodium hyaluronate). The following parameters were used to evaluate pain relief and safety: visual analog scale (VAS) for pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and side effects before the injection and at 1, 2, and 5 weeks after treatment commencement as well as 3 months after the last injection.

Results: Patients from both groups had a significant improvement in VAS and WOMAC scores from the first injection to final follow-up at 3 months. In the first week, the VAS score was lower in group A ($P = .041$), but no significant between-group differences were found for either the VAS or the WOMAC score at the other time points. Of the 42 patients in group A, 34 (81.0%) and 25 (59.5%) achieved successful outcomes at 5 weeks after treatment commencement and 3 months after the last injection, respectively. In group B, 32 (76.2%) and 24 (57.1%) patients achieved successful outcomes at 5 weeks after treatment commencement and 3 months after the last injection, respectively. At final follow-up, no significant difference was found in the successful treatment rate between the groups ($P = .825$).

Conclusion: The current study demonstrated that intra-articular ketorolac and corticosteroid injections produce the same pain relief and functional improvement.

Keywords: intra-articular injection; ketorolac; corticosteroid; knee osteoarthritis

Primary knee osteoarthritis (OA) can progress and cause severe pain and functional impairment for patients. Pain relief and functional improvement are the main therapeutic goals for knee OA. To date, there are many treatment choices such as physical, pharmacological, and surgical approaches.

Intra-articular corticosteroid injections have been considered a mainstay in the nonoperative treatment of symptomatic knee OA. They can significantly reduce local inflammatory reactions and pain levels. However, their increased use can have negative implications such as chondral toxicity, which results in cartilage breakdown and loss

The Orthopaedic Journal of Sports Medicine, 8(4), 2325967120911126
DOI: 10.1177/2325967120911126

of articular cartilage elasticity along with a high risk of infections.[5,22]

An inflammatory reaction has been demonstrated as the main factor contributing to the symptoms and progression of OA.[20] Nonsteroidal anti-inflammatory drugs (NSAIDs) have been considered as an alternative in intra-articular injections. These injections have strong anti-inflammatory effects and fewer adverse reactions as compared with steroid injections. Considering the disturbance of normal platelet function and gastrointestinal toxicity, local utilization may supply higher tissue concentrations with fewer systemic complications.[17]

To the best of our knowledge, there has been little research concerning intra-articular NSAID injections for symptomatic knee OA. The primary aim of this study was to compare the differences in pain relief and function for patients with knee OA receiving either an intra-articular ketorolac or corticosteroid injection. The short-term safety of an intra-articular ketorolac injection was also investigated as a secondary endpoint. We hypothesized that an intra-articular ketorolac injection would reduce local inflammatory reactions and improve pain levels and knee function.

METHODS

This case-control, retrospective comparative study was approved by an ethics review committee. All patient information and identifiers were removed and remained confidential during the research study. The study was carried out in accordance with approved guidelines.

From July 2014 to October 2016, a total of 84 outpatients (50 female and 34 male) with unilateral symptomatic knee OA (Kellgren-Lawrence[11] grades 2 and 3), aged 48 to 72 years (mean age, 58.5 ± 10.9 years), were enrolled in this retrospective study. All patients had undergone pharmacological or physical therapy for at least 3 months with no improvement. All enrolled patients had previously been randomly allocated using a random number table to receive intra-articular corticosteroid or ketorolac injections. According to the treatment received, half of the cohort was divided into group A (intra-articular corticosteroid injection; n = 42) and half into group B (intra-articular ketorolac injection; n = 42). The exclusion criteria applied were inflammatory knee arthritis, significant autoimmune diseases, any injection in the knee 3 months prior, and severe neurological or psychiatric diseases that made it difficult to participate in the study.

TABLE 1
Baseline Characteristics (N = 84)[a]

	Group A	Group B	*P* Value
Age, y	58.16 ± 10.21	59.02 ± 11.25	.530
Sex, male/female, n	16/26	18/24	.824
Body mass index, kg/m^2	18.76 ± 1.79	18.85 ± 1.67	.139
Kellgren-Lawrence grade 2/grade 3, n	27/15	26/16	.821
Laterality, left/right, n	14/28	11/31	.634
Pain duration, mo	8.35 ± 3.86	8.59 ± 4.32	.625
VAS pain score	7.24 ± 0.88	7.43 ± 0.80	.302
WOMAC score	46.60 ± 4.29	47.83 ± 4.07	.179

[a]Data are shown as mean ± SD unless otherwise indicated. VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Intra-articular Injection Regimen

All patients received 5 weekly intra-articular injections by the same physician using aseptic procedures. Triamcinolone acetonide/ketorolac was given during the first 3 weeks. In the last 2 weeks, patients only received intra-articular sodium hyaluronate. Imrecoxib (100 mg orally twice daily; Jiangsu Hengrui Medicine) was administered as a primary analgesic treatment for 3 days. The oral analgesic regimen was permitted after each injection, and other oral analgesics during the study period were prohibited. Medications other than those for pain were permitted so that patients could maintain their regular therapy.

All the parameters were evaluated and recorded at 1, 2, and 5 weeks after treatment commencement and 3 months after the last injection. The physicians responsible for the evaluation were unaware of each patient's group and therapeutic regimen during the entire research period. All the intra-articular injections were performed by the same orthopaedic surgeon with a superolateral approach[24]:

- Group A: a 10-mL intra-articular injection of a mixed drug regimen (5 mL of 0.5% lidocaine and 25 mg of triamcinolone acetonide) + 2.5 mL of sodium hyaluronate (25 mg; Shanghai Chenfeng Medicine).
- Group B: a 10-mL intra-articular injection of a mixed drug regimen (5 mL of 0.5% lidocaine and 10 mg of ketorolac) + 2.5 mL of sodium hyaluronate (25 mg; Shanghai Chenfeng Medicine).

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Final revision submitted October 28, 2019; accepted December 12, 2019.
The authors declared that there are no conflicts of interest in the authorship and publication of this contribution. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.
Ethical approval for this study was obtained from the Ethics Review Committee of Changzhou Traditional Chinese Medical Hospital, affiliated to Nanjing University of Traditional Chinese Medicine.

TABLE 2
VAS Pain Scores[a]

	Before Injection	1 wk	2 wk	5 wk	3 mo	*F* Value	*P* Value
Group A	7.24 ± 0.88	2.46 ± 0.73	2.31 ± 0.64	2.40 ± 0.59	2.20 ± 0.52	1.388	.242
Group B	7.43 ± 0.80	2.86 ± 0.81	2.21 ± 0.68	2.28 ± 0.47	2.26 ± 0.63		
P value	.302	.041	.512	.305	.706		

[a]Data are shown as mean ± SD. VAS, visual analog scale.

TABLE 3
WOMAC Scores[a]

	Before Injection	1 wk	2 wk	5 wk	3 mo	*F* Value	*P* Value
Group A	46.60 ± 4.29	34.05 ± 5.20	25.24 ± 4.55	21.24 ± 2.14	22.81 ± 4.46	0.432	.513
Group B	47.83 ± 4.07	31.71 ± 5.59	25.29 ± 4.51	21.79 ± 2.18	21.98 ± 4.35		
P value	.486	.274	.692	.342	.186		

[a]Data are shown as mean ± SD. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Clinical Parameters

The follow-up duration was defined as the time between the first injection and the recording time. The side effects and complications (evaluated just from a clinical examination) were also recorded. The baseline characteristics were documented: age, sex, body mass index, Kellgren-Lawrence grade, side of knee OA, pain duration and pain visual analog scale (VAS) score, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score before the injection; there were no significant differences between groups at baseline (Table 1).

Pain intensity (rest/movement) was assessed using a 10-cm horizontal VAS,[21] with 0 cm indicating "no pain" and 10 cm indicating "worst pain." Pain at rest was assessed after a 30-minute rest. The WOMAC was employed to evaluate knee function.[2] The overall response to treatment was evaluated by the Rubin scale (1 = poor; 2 = fair; 3 = good; 4 = excellent).[18] Successful treatment was defined as a Rubin score of good or excellent. The successful treatment rate was calculated using the following formula: n1(good + excellent)/n × 100%.

Statistical Analysis

SPSS (Version 17.0; IBM) was employed for statistical analyses. The normality of distribution for continuous numeric variables was assessed using the Kolmogorov-Smirnov test. Normally distributed variables are presented as means with standard deviations. The characteristics of the 2 groups were analyzed by the Student *t* test, chi-square test, or Wilcoxon rank-sum test. At each time point, VAS and WOMAC scores were compared by repeated-measures analysis of variance. $P < .05$ was considered to indicate statistical significance.

RESULTS

All the patients from both groups had a significant improvement in their VAS and WOMAC scores from the first injection to latest follow-up. No patients were lost to follow-up. Of the 42 patients in group A, 34 (81.0%) and 25 (59.5%) achieved successful outcomes at 5 weeks after treatment commencement and 3 months after the last injection, respectively. In group B, 32 (76.2%) and 24 (57.1%) achieved successful outcomes at 5 weeks after treatment commencement and 3 months after the last injection, respectively. At latest follow-up, no significant differences were found in the successful treatment rate as defined by the Rubin scale between these 2 groups ($P = .825$).

Pain Findings

The mean VAS pain scores of both groups decreased significantly from baseline to each follow-up time point. At the first week, the VAS score was lower in group A ($P = .041$), but no significant differences were found at any other time point (Table 2).

Functional Results

The mean WOMAC scores of both groups A and B decreased significantly from baseline to latest follow-up ($P < .001$). There were no significant differences between the 2 groups at each time point (Table 3).

Complications

No serious complications were found in either group. Only 3 patients in group B developed mild, focal postinjection pain for about 1 to 3 days. All pain complaints were self-limited and subsided with no supplemental treatment.

DISCUSSION

In this study, we confirmed that intra-articular ketorolac injections provided the same pain relief and functional

improvement as intra-articular triamcinolone acetonide injections. Also, no serious complications were found in either group.

Hyaluronic acid, present in synovial fluid and cartilage, has been widely accepted as a viscosupplement for the treatment of knee OA pain. It imparts viscoelastic properties that allow for the efficient movement of articular joints. Huang et al[10] conducted a randomized, double-blind, multicenter placebo-controlled study to evaluate the efficacy and tolerability of sodium hyaluronate for the treatment of knee OA. Also, the researchers suggested that 5 weekly intra-articular injections of sodium hyaluronate are well tolerated, can provide sustained relief of pain, and improve function. Altman et al[1] also evaluated the safety of sodium hyaluronate for painful knee OA. They founded that repeat injections of sodium hyaluronate were effective, safe, well tolerated, and not associated with an increase in adverse events.[1] Based on a Chinese expert consensus (2012 edition),[14] all patients received intra-articular injections of sodium hyaluronate in our present study. It is possible that some or all of the benefits seen in our patients were a result of sodium hyaluronate.

While primary knee OA is not a classic inflammatory arthropathy, it is usually associated with inflammation. This inflammatory reaction is the main factor contributing to the symptoms of pain and the progression of OA. Some inflammatory cytokines such as bradykinin or histamine can directly stimulate the primary afferent nociceptive fibers, while others can decrease the pain threshold via sensitizing the primary afferent nociceptive fibers to stimulus.[4] Additionally, synovitis is considered an early feature in OA and is not just found in advanced OA. Synovial inflammation can exacerbate structural damage and pain levels because of the production of inflammatory cytokines, which results in the release of degradative enzymes and modulates pain perception.[3,12]

As a main nonoperative therapy, intra-articular corticosteroid injections can significantly reduce inflammation and relieve pain via a minimally invasive method. The overall anti-inflammatory mechanism of action for a corticosteroid is multifactorial: in general, it inhibits antigen opsonization; cell adhesion and migration; and the synthesis and release of cytokines, leukotrienes, prostaglandins, and neutrophil superoxide.[23] In the current study, of the patients who received corticosteroid injections, 34 (81.0%) and 25 (59.5%) achieved successful outcomes at 5 weeks after treatment commencement and 3 months after the last injection, respectively. In a review by Hepper et al,[9] intra-articular corticosteroid injections demonstrated a statistically and clinically significant reduction in pain when compared with placebo. However, their increased use can have negative implications including chondral toxicity and a high risk of infections.

Ketorolac has been recognized as a promising pain reduction medication. Within the past decade, it has been widely used in arthroscopic surgery and arthroplasty alone or combined with other agents. After shoulder arthroscopic surgery, adding ketorolac to intra-articular analgesia injections has been recognized as a safe and effective method to improve pain relief.[26] In this study, intra-articular ketorolac injections demonstrated similar pain relief and functional benefits compared with intra-articular cortisone injections. Overall, no significant differences were found in the successful treatment rate between these 2 groups.

The safety of intra-articular corticosteroid injections is still controversal.[8] Side effects associated with intra-articular corticosteroid injections do exist. Other known complications include an increased incidence of joint infections, skin atrophy, and tendinopathy. Although cortisone injections may increase a patient's risk for an infection and chondral damage, it is broadly perceived among clinicians that complications after a joint injection are indeed rare.[15] A survey of orthopaedic surgeons was used to quantify the perceived risk of infections after a joint injection. Half of 853 surgeons perceived the risk of infections as 1 in 1000 injections, and 33% perceived the risk as even lower, at 1 in 10,000.[7] Considering the negative potential side effects, some researchers have suggested that the frequency of steroid injections should be less than once every 3 months.[25] A clinical trial by Raynauld et al[16] examined the effect of 40 mg of triamcinolone acetonide in patients with OA by administering injections every 3 months for 2 years. Long-term triamcinolone acetonide administration prevented narrowing of the radiographically measured joint space over a 2-year study period.[16] Based on clinical experience, we choose 3 weekly injections of intra-articular corticosteroid over the 5-week injection period to prevent possible cartilage damage.

As an alternative choice, ketorolac shows some clinical safety. Intra-articular ketorolac injections have produced degenerative changes noted microscopically just like normal saline. No obvious cartilage necrosis has been found after a ketorolac injection.[19] The use of intra-articular ketorolac might be safe and do less harm to local tissues.[19] Dogan et al[6] found that mild histopathological changes might be found in rabbit knee joints after an intra-articular morphine or ketorolac injection, but safety was confirmed when used intra-articularly. In the present study, only 3 patients in group B developed focal postinjection pain for about 1 to 3 days. All of the pain complaints were self-limited and subsided with no supplemental treatment. Lee et al[13] pointed out that focal postinjection pain was associated with local ketorolac concentrations. To date, a consensus about the optimal concentration and amount of ketorolac has not yet been reached and should be determined by further studies.

There were some limitations to the present study. All patients received sodium hyaluronate, and the benefits seen in both groups could be attributed to that. Ideally, a study comparing only triamcinolone acetonide with ketorolac would be needed for a true comparison. There were some other limitations in our study. First, this was a retrospective study in design, but the extensive inclusion and exclusion criteria described controlled the shortcomings. Second, the radiographic results of cartilage degeneration were not followed up. Thus, it is unknown whether there was any difference in the progression of cartilage degeneration in either group. Third, the follow-up period was just 3 months. The short follow-up reflected the efficacy of the single treatment and avoided the influences of other

procedures; however, it does not give information on the possible long-term effects of the injections.

The current study shows that when combined with sodium hyaluronate, intra-articular ketorolac produced the same pain relief and functional improvement as corticosteroid at 3 months after an injection. Further prospective controlled trials are necessary, however, to make any definitive treatment recommendations.

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